AREA OF EMPHASIS:

Etiology and Pathogenesis

SCIENTIFIC ISSUES

In the quest for vaccines and microbicides to prevent HIV infection and for more effective drugs and immune-based therapies to contain the infection and treat the opportunistic infections (OIs), tumors, and other manifestations of a dysfunctional immune system, a better understanding is needed of two areas: (1) how HIV infection is established and maintained, and (2) what causes the profound immune deficiency and severe clinical complications that accompany this infection. This understanding will come from the knowledge gained in answering the following questions. What role do specific HIV proteins play in the viral life cycle in individual cells and within the bodies of infected individuals? What are the primary modes of HIV transmission between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other organ systems affected by HIV? What host factors and cofactors influence primary infection and the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, OIs and coinfections, neurological impairments, and metabolic disturbances that characterize AIDS? These outstanding questions define the central contemporary issues encompassed within the area of HIV etiology and pathogenesis research.

HIV BIOLOGY

PRIORITY FOR FUTURE RESEARCH:

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection. Identify and validate cofactors for viral genes as new targets capitalizing on novel technologies including RNA interference and genomic screening.**

Since the initial isolation of HIV in 1983 and its identification as the causative agent of AIDS shortly thereafter, tremendous progress has been made in understanding the genetic structure and variability of the viral genome, the critical aspects of the virus life cycle, and the function of viral gene products and their interaction with the host. The knowledge that has emerged from basic research in these areas has provided and continues to provide the foundation for all efforts to develop current therapies to treat HIV infection. The elucidation of the structure and function of critical viral enzymes—reverse transcriptase, protease, and integrase—has represented a critical step in the development of effective anti-HIV drugs. Similar insights from NIH-funded basic research into the mechanisms of viral entry and the mechanisms by which the infection becomes established and spreads have provided the basis for a new generation of antiretroviral (ARV) drugs that is just being developed and introduced, and also are crucial for vaccine and microbicide development efforts. Even though HIV has been under intense investigation for two decades, NIH-funded research continues to make major breakthroughs, such as the mechanism of action of the critical Vif protein and its cellular cofactors. The recent discovery of innate host antiviral resistance factors such as APOBEC3G and TRIM5α will provide other important targets for novel ARV agents. The challenges remain to develop new drugs for the treatment of HIV infection that are less expensive, easier to take, more potent, with complementary mechanisms of action that lead to more complete suppression and with fewer adverse effects than those currently in use, along with microbicides to prevent sexual transmission of HIV infection, and to identify immunogens able to elicit strong cellular and neutralizing responses for the development of an effective vaccine.

Scientific advances in AIDS research, such as the resolution of the structure of gp 120 protein before it binds to the CD4 on the surface of target cells, discovery of a novel myristyl switch mechanism that regulates intracellular targeting of the HIV-1 matrix protein, the identification of conformational changes in the HIV-1 capsid protein that accompany viral maturation, the discovery of antiviral agents that inhibit HIV-1 capsid assembly, the delineation of many of the molecular interactions between virally encoded regulatory proteins and host cell factors, recent insights into critical requirement for viral attachment and replication, viral budding and release from cells, and the identification of conserved structural intermediates of gp41 that might be able to elicit a strong and cross-reactive neutralizing response are affording us the opportunity to identify new viral and cellular targets for therapeutic and preventive

interventions. New technologies like genomic screening and transcriptional gene silencing by small interfering RNAs will be instrumental in validating new targets and prioritizing drug discovery candidates.

Emphasis should be placed on the elucidation of structures and a better understanding of the biochemistry, interaction, and biologic function of relevant virus and host cell constituents. Structures have been determined for some individual HIV proteins, but there is currently very little structural information on any of the regulatory and accessory HIV proteins (Tat, Rev, Vif, Nef, Vpr, and Vpu). There is also the need to obtain structural and dynamic information on how these proteins interact with each other and their cognate host-cell proteins. Collaborations between biochemists and structural biologists to define the interactions of HIV proteins with their cognate host-cell partners and determination of the three-dimensional structures of these complexes should be promoted.

The NIH should play an instrumental role in facilitating collaborative research aimed at developing and implementing biologically relevant validated assays for drug screening as new targets are identified.

TRANSMISSION, ESTABLISHMENT, AND SPREAD OF HIV INFECTION

PRIORITY FOR FUTURE RESEARCH:

- **Elucidate the biologic determinants of HIV transmission between individuals, and define the mechanisms by which host factors, viral factors, and cofactors may influence the process of HIV transmission and dissemination.**

The early interaction of HIV with target cells at the portal of entry is critical for the subsequent establishment and spread of infection. This has become even more important with the increasing recognition of the transmission of drug-resistant variants of HIV. However, in spite of the tremendous scientific advances in AIDS research, the factors that determine the transmissibility of HIV and the variables that may influence a person's susceptibility to HIV infection following exposure have yet to be clearly understood. The observed resistance to HIV-1 infection of multiply exposed subjects bearing a homozygous deletion in one of the genes encoding a chemokine coreceptor for primary HIV-1 isolates highlighted the importance of coreceptors in HIV-1 transmission.

Why CCR5-using HIV variants predominate during initial infection remains unclear, and answering this question will be critical for understanding essential mechanisms of transmission and developing prevention strategies. Similarly, other host genetic polymorphisms have been identified that influence transmission, and unraveling how and why they affect viral spread will facilitate the development of therapeutic and preventive strategies.

Prospective studies in discordant couples have provided evidence that peripheral blood viral load is the most important predictor of the risk of heterosexual transmission of HIV. These findings have important implications for the development of prevention strategies, since they suggest that reducing viral load in HIV-infected persons will result in their decreased infectiousness. In the same studies, circumcision also appeared to protect against acquisition of HIV, highlighting the role of host factors as well as behavior in HIV transmission.

NIH-funded research is giving special emphasis to studies aimed at defining the role of components of the mucosal compartment, cellular and molecular aspects of mucosal innate and adaptive immunity, viral heterogeneity, disease stage, viral genotype/phenotype/clade, hormones, cofactors such as other infectious agents, including sexually transmitted infections (STIs), and systemic and local inflammatory processes on the ability of infected individuals to transmit HIV. The factors affecting susceptibility or resistance to HIV acquisition including coreceptor expression, innate and adaptive immune responses, hormones, vaginal flora, STIs, and inflammatory processes are also studied by NIH-funded investigators. Systemic and genital tract inflammation has a major effect on HIV acquisition since it results in an increased expression of viral receptors on target cells, recruitment of target immune cells from the circulation, and increased permeability of the epithelium. The ability to support active local replication and subsequent establishment and spread of infection might also depend on the local inflammatory milieu.

This basic knowledge is crucial for our efforts to develop effective vaccines and microbicides. In the developing world, where infection rates have climbed to more than 20 percent in some countries and few people can afford antiretroviral therapy (ART), the main issue continues to be how to stop transmission of the virus by effective preventive interventions.

Emphasis should be placed on studies focused on cohorts that are most representative of the expanding HIV epidemic. This can be facilitated by studies whose designs reflect the collaborative interaction of basic scientists and population-based researchers. Efforts should also be directed at understanding the relative efficiency of transmission of cell-free and cell-associated virus in various bodily fluids at different portals of entry (particularly mucosal), mechanisms and timing of initial entry, the cells that represent the first target of infection, mechanisms of virus compartmentalization in genital secretions, the relationship between biologic findings and the anatomical organization of mucosal tissue, and the role of viral genotypes/phenotypes and dose on HIV entry and establishment of infection. The NIH also recognizes the critical need for a better understanding of the mechanisms involved in mother-to-child transmission and transmission through breastfeeding, which both represent major modes of transmission. Emerging technologies in genetics, computational biology, *in vivo* imaging, functional genomics and proteomics, and the assessment of host

immune responses should also be brought to bear on studying the biology of HIV transmission.

Emphasis should continue to be placed on the recruitment of recently exposed subjects (whether they become HIV-infected or not) to gain a better understanding of the mechanisms of resistance to infection and the early events leading to transmission and dissemination.

PATHOGENIC MECHANISMS OF HIV INFECTION

PRIORITY FOR FUTURE RESEARCH:

- **Understand the dynamic of virus-host interaction through the course of HIV infection.**

Many factors regulate the dynamics of virus replication and host responses. Characterizing these factors *in vivo* and determining how they change over the course of infection; how they are influenced by age, ethnicity, sex, gender, and health status; and how they differ in international settings with different viral, host, and environmental influences have great implications for a better understanding of the effects and nature of the host response to HIV, the processes leading to the loss of control of HIV replication, and the pathogenesis of AIDS.

Interaction of HIV with its host is a dynamic process that varies through the course of infection, from the very early to the late stages. Both viral and host factors are clearly critical in regulating this relationship, including the virus, genotypic, phenotypic, and fitness characteristics and host genetic and immunological factors. Soon after infection, a viral setpoint is established, which has a major role in determining the later course of disease. The factors that determine this setpoint have yet to be established, and this is an important focus of investigation. CD4+ T helper cell activity diminishes rapidly after primary HIV infection and is only partially restored by effective antiviral therapies administered at a later time. Different CD8 epitopes are targeted by cytotoxic T lymphocyte (CTL) in acute versus chronic infection, and both CD4 and CD8 responses change before and after the establishment of the viral setpoint. In addition, HIV-1-specific CD8+ T-cell responses differ in their ability to drive viral escape by sequence variation.

NIH-funded research conducted at the molecular, cellular, tissue, and organ system levels is elucidating the pathogenic mechanisms associated with HIV infection. Investigators are focusing on studies of the mechanisms by which HIV infects various cell types, the interaction between the viral regulatory elements and host cell factors that maintain a persistent infection, and the viral- and host-mediated mechanisms that influence the level of viral expression seen in progressive stages of HIV disease. Since HIV so profoundly affects the immune system, ongoing research is also aimed at elucidating the viral- and immune-mediated pathogenic processes that result in the severe loss of immune function, inappropriate immune activation, and disruption of

immunomodulatory cytokine production and regulation observed in HIV infection and disease. Data have shown that HIV preferentially infects HIV-specific CD4+ T cells during the process of immune recognition and response, thereby providing a potential mechanism to explain the predominant loss of HIV-specific CD4 T-cell responses and consequently the loss of immunologic control of HIV replication.

NIH-supported investigators have demonstrated that significant levels of virus are present in plasma during all stages of HIV infection, including the clinically asymptomatic phase, and that active virus replication is linked directly to the depletion of T-cell populations and is correlated with progression to disease. This model of AIDS pathogenesis would imply that HIV induces disease by replicating at high levels in CD4+ T cells, eventually weakening the immune system and causing it to fail. However, simian immunodeficiency virus (SIV) replicates at high levels in the infected natural hosts of African green monkeys and sooty mangabeys without causing significant symptoms or disease, clearly indicating that high levels of viremia do not necessarily lead to disease. Therefore, host factors or the particular nature of the host response play a critical role in determining whether and when disease arises following infection. The emphasis on the dynamic and quantitative aspects of HIV replication is paralleled by efforts to quantify T-cell population dynamics *in vivo* during different stages of HIV infection and disease. It is also important to elucidate the aspects of innate and adaptive immunity that serve to control viral replication in tissues, recognizing that observations made using peripheral blood lymphocytes may not necessarily be extrapolated to tissues. These efforts have great implications for understanding the mechanism behind the most central and unresolved issues in HIV-mediated immunopathogenesis: the depletion of CD4+ T cells and the failure of the regenerative capacity of the immune system to compensate for virus-induced damage. Several mechanisms, either direct or indirect, have been suggested; however, the critical mechanisms remain to be elucidated. New technological developments that permit the measurement of lymphocyte population dynamics and numbers of cells recently emigrated from the thymus during HIV infection, disease, and therapy are providing valuable insights into this pathogenic process. Innovative techniques for *in vivo* imaging also will provide crucial information on tissue reservoirs and compartments of HIV infection associated with viral replication. Elucidation of these mechanisms will be critical for generating new therapeutic principles and approaches that will take into account both viral and cellular kinetic parameters.

In the last several years, NIH-funded research has identified multiple host genetic determinants that influence both the level of viral replication and host immune responses, and have a great impact on disease progression. New discoveries regarding the host machinery used by the virus for replication open the possibility of additional host polymorphisms that may exist, as well as providing novel therapeutic targets. Viral phenotypes that have a powerful impact on the course of disease have been identified, but a true understanding of viral determinants of replication *in vivo*

and viral fitness requires further clarification. Finally, the role of copathogens in regulating the virus-host dynamic is a critical area of further study. Importantly, these factors will also vary in nature and relative importance at different stages of disease, and will also differ in international settings based on distinct host genetic, viral genetic, and environmental influences.

Gender, sex, health status, race, and age affect the biology of HIV infection and the immune response to HIV, as well as the responses to therapies and vaccines. The basic science underlying HIV etiology and pathogenesis research is considered to be sex- and gender-neutral. Basic mechanisms of viral replication and viral-induced pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease is manifested in women and men. In addition, it is well recognized that induced autoimmune phenomena are more prevalent in the general population of women. Moreover, recent studies have highlighted differences in viral dynamics in women compared with men, and further studies are warranted to elucidate the biological underpinnings for these findings. Efforts should be made to integrate knowledge from disciplines such as reproductive biology, mucosal immunity, and endocrinology to the study of sex and gender differences in HIV infection. It will be important to understand elements of innate and adaptive immunity that function to control viral replication in tissues of the male and female reproductive tract. Some of the studies that examine sex and gender differences compare factors other than sex in patients. HIV-infected women are more likely to be poor, to belong to racial minorities, to be of poor health status, and to use injection drugs. These are all factors that might have important effects on health outcomes for both men and women infected with HIV. Age also is emerging as another important factor to consider, due to the increased survival of HIV-infected persons and the increased number of newly HIV-infected individuals at different life stages.

PRIORITY FOR FUTURE RESEARCH:

- **Investigate the mechanisms of persistence of HIV infection.**

The dramatic success of effective ART in reducing plasma viremia to undetectable levels had profound clinical benefit, but HIV rebounds very quickly upon discontinuation of therapy, and the virus can persist in HIV-infected patients, perhaps indefinitely, and thus eradication remains a critical but elusive goal. HIV can persist through continued low-level replication, even in the presence of ART that is able to drive viremia below the limits of detection, and in a latent reservoir of resting memory CD4+ T cells that is established very early after infection. Persistent ongoing viral replication may explain the apparent long half-life of the latently infected reservoir, since this replication could be reseeded continuously from activated CD4+ T cells and monocytes/macrophages newly infected with HIV. Monocytes and macrophages, as well as natural killer (NK) cells, the brain, the rectal mucosa,

and the renal epithelial cells appear to represent reservoirs for viral persistence in patients on ART. We still do not know how many different cells and tissue types may represent potentially important reservoirs of HIV or their relative contribution to viral replication rebound following treatment failure or discontinuation. Residual viral replication is a complex phenomenon and probably involves more than one mechanism. A better understanding of the different mechanisms of viral persistence is needed to discern the reasons for drug failure, to design rational approaches for virus control or eradication, and to better assess the impact of virus persistence on HIV transmission and its implications for HIV prevention.

Research efforts should focus on the explication of cells, tissue reservoirs, and compartments of HIV latency and/or residual replication during suppressive ART, their rates of turnover, the mechanisms of viral latency and reactivation, the impact of low-level viral replication on virus transmissibility, and the ability of natural and induced immunity to control and potentially eliminate persistent infections. Studies directed toward identifying the origin of virus rebound in patients who have stopped therapy, the contribution of virus from latently infected cells and/or residual replicating virus to virus rebound, the best cellular and molecular techniques to measure HIV-1 reservoirs and ongoing replication *in vivo*, and approaches to purge these reservoirs and compartments of virus are also of particular importance. Development of *in vitro* models of HIV proviral latency and *in vivo* models of HIV residual disease will be beneficial in answering remaining questions in this field.

PRIORITY FOR FUTURE RESEARCH:

- **Develop innovative technologies in human and nonhuman primate (NHP) immunology to guide HIV prevention and immune reconstitution efforts in HIV-at risk/infected individuals.**

Elucidation of the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to the design of rational immune reconstitution approaches in persons undergoing ART and to identifying the characteristics of the immune response that are needed for a protective vaccine. It is important to acquire this knowledge for all the populations affected by HIV: men and women throughout their lifespans and for all racial and ethnic backgrounds.

Emphasis should be placed on obtaining a better understanding of the immunologic components and responses present in mucosal surfaces and the anatomical compartmentalization of immune responses. The prerequisites for induction of mucosal immunity have not been well defined in the human. Thus, special attention should be paid to understanding the elicitation of mucosal immune responses and the trafficking of cells between peripheral immunological sites and mucosal sites, as

well as the trafficking between distal mucosal compartments and innate immunity. The importance of the early events (first days or weeks) following HIV infection has stimulated interest in understanding the innate immune responses and the interface between innate and adaptive immunity. These areas have been largely unexplained in HIV/AIDS research and could have major implications for vaccines and microbicides development.

Emphasis should also be placed on a better understanding of the elicitation and maintenance of immunologic memory and on the definition and validation of markers and assays that will enhance our understanding of and ability to study immune function in humans, especially those approaches that permit the study of *in vivo* regulation and function of the immune system. Recent technological breakthroughs are affording us the opportunity to assess more accurately the quantity and function of T cells in HIV infection, the impact of these T-cell responses on viral sequence evolution, and the ability of the virus to escape from T-cell-mediated immune pressure by sequence variation within targeted epitopes. The use of these innovative techniques is providing investigators with critical insights into the effects of HIV infection, viral sequence evolution, ART, and potential preventive or therapeutic vaccines on the immune system. Our attempts to preserve or reconstitute the immune function in HIV-infected persons will benefit also from focused efforts directed at elucidating the homeostatic and regenerative mechanisms of various lymphocyte populations, the markers for true thymic-derived cells, the factors that may influence T-cell proliferative capacity or survival in the normal state and in HIV disease, the immunological impact of long-term therapies, and potential interventions to improve thymic function and the generation of naive T cells. Potential compensatory mechanisms to replenish T cells lost during infection include peripheral expansion of residual memory cells and increased production of naive cells by the thymus. Current effective ART leads to a rapid increase in circulating memory CD4+ and CD8+ T cells, probably due to redistribution from lymphoid organs, a decrease in cell death, and peripheral expansion. However, reconstitution of the T-cell repertoire is generally delayed for many months and may ultimately require production of new T cells from the thymus.

Focused efforts directed at characterizing the functional diversity of CD4+ and CD8+ memory and effector cells, at analyzing humoral and cellular immunity in microenvironments (especially at mucosal sites), and at an enhanced understanding of mechanisms leading to maintenance of immunological memory will greatly benefit research aimed at the development of effective HIV vaccines. In addition, advances in technology are increasing our awareness of cell subsets, including regulatory T cells, natural killer T (NKT) cells, and distinct functional subsets of dendritic cells (DC) and macrophages, whose roles in antiviral immunity are not yet well understood. The study of immune escape is of great importance to our understanding of pathogenesis, as well as to the development of a successful HIV vaccine. Efforts

should be directed toward increasing our understanding of mechanisms of immune escape from CTL and neutralizing antibodies in NHP models and in HIV infection. It is becoming apparent that superinfections are becoming more common than was previously appreciated and understanding how the immune response fails to protect from infection with related pathogenic viruses is also very important.

Continued support of *in vivo* research is a high priority at the NIH to further an understanding of the interactions between the virus and host immune system response. NIH-sponsored longitudinal cohort studies constitute a major resource for pathogenesis research. Specific cohorts, such as long-term nonprogressors, HIV-exposed but uninfected individuals, and rapid progressors, will provide clues for treatment and vaccine research by helping to characterize immune response profiles and by providing information on correlates of immunity. *In vivo* research into mechanisms of virus-mediated immunopathogenesis also utilizes animal models. All the available animal models, but in particular the NHP models, have contributed and continue to contribute to our understanding of disease mechanisms. Development and distribution of reagents for immunologic studies in NHPs, as well as overlapping peptide reagents for epitope mapping of both SIV and HIV, are essential for continued progress in these models.

DISEASE MANIFESTATIONS

HIV infection affects the functioning of virtually all the organ systems within the body. Current NIH-supported basic and clinical studies are focused on the characterization of HIV/AIDS-associated diseases and on the assessment of their relative contribution to the overall disease progression in AIDS. The NIH is striving to enhance the bidirectional flow between basic and clinical observations and intervention programs on HIV-related complications.

PRIORITY FOR FUTURE RESEARCH:

- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of ART and the factors that underlie changes in the causes of morbidity and mortality in HIV-infected patients in an era of increasingly effective therapies.**

The availability of new and more effective antiviral drugs and treatment modalities is having a beneficial effect on the course of HIV infection and has altered the incidence and nature of some of its manifestations. The influence of ART, which is able to lower viral load to undetectable levels, on the natural history of AIDS is providing an unprecedented opportunity to gain insights into the pathogenic mechanisms underlying the disease manifestations associated with HIV infection and AIDS. Unfortunately, use of these therapies also is associated with a series of side effects and complications that we are just starting to appreciate and study. Although most metabolic complications were initially blamed on ART, it is now clear that other factors, mainly HIV disease, may contribute to their development.

Assessing the time line, absolute risk, and severity of outcome for these complications is essential for an effective clinical management of HIV-infected patients.

Metabolic and Body Composition Changes

The study of HIV-associated manifestations is rapidly changing as a result of the introduction of effective ART and the concomitant decline in the incidence of OIs. The incidence of wasting has declined, and hyperglycemia, insulin resistance, diabetes, hypercholesterolemia, hypertriglyceridemia, and fat redistribution (either depletion or accumulation) have been described in HIV-infected individuals taking ART. These manifestations are a real cause for concern with broad public health implications. Patients are experiencing problems in adhering to regimens when these symptoms occur: some stop taking medications, and others are not initiating therapies due to the possible occurrence of disfiguring physical changes and the long-term risk of cardiovascular complications. These changes were initially considered a single syndrome commonly referred to as lipodystrophy. Recent data are instead suggestive of multiple syndromes with different etiologies. Protease inhibitors were first associated with these metabolic and body composition changes, but recent data have indicated that HIV patients treated with only nucleoside reverse transcriptase inhibitors (NRTIs) also develop many of these symptoms. In addition to the direct effects of these drugs, age, duration of therapy, HIV disease, and return to health following suppression of viral replication also may play a role in the development of these abnormalities. With the longer duration of therapy, many other complications have been reported in association with current anti-HIV treatment including bone disease, lactic acidosis, pancreatitis, and liver toxicities. Mitochondrial damage and depletion resulting from the inhibitory activity against gamma DNA polymerase of some of these drugs could potentially be involved in the etiology of some of these complications. Several complications might be due to the host response to HIV infection, as it occurs as a result of other chronic infections. Studies of the immune response to HIV in untreated and ART-treated subjects should incorporate assessment of metabolic parameters. As ART is introduced into the developing world, studies should address the metabolic complications of long-term treatment and survival in that setting, including host determinants of these complications.

Elucidation of the factors contributing to metabolic and body composition changes, toxicities, and long-term consequences of ART will allow effective therapies to be tailored to the specific mechanism by which they occur, with the potential for enhancing quality of life in HIV-infected persons.

Although the incidence of wasting has declined in the developed world, it remains one of the most devastating aspects and one of the major causes of morbidity and mortality in HIV-infected individuals who do not respond or lack access to potent ART, an issue in the developing countries. Weight loss in AIDS results in a significant

reduction in survival, independent of other influencing factors, including CD4+ cell count and history of infection or malignancy.

The introduction of effective ART has changed the natural history of HIV infection and has led to a dramatic decline in morbidity and mortality in HIV-infected persons in developed countries. However, anti-HIV therapy is not a cure and does not successfully benefit every infected individual. End-stage liver disease and liver failure are becoming an increasing cause of mortality in HIV-infected patients. However, since multiple concurrent causes of liver damage are associated with HIV infection, including hepatitis viruses coinfection, ARV hepatotoxicities, OIs, and cancers, the impact of each cause of liver injury on a patient's survival in an era of effective therapies is unclear.

Epidemiological studies in large cohorts will be instrumental in identifying changes in the causes of morbidity and mortality as a result of the availability of effective therapies in HIV-infected communities and in providing us with useful insights into their etiologies.

AIDS-Related Malignancies

AIDS is associated with a broad spectrum of neoplasms, including Kaposi's sarcoma (KS); lymphomas; human papillomavirus (HPV)-related, oral, cervical, and anogenital carcinomas; Castleman's disease; leiomyomas; leiomyosarcomas; and hepatitis B-related hepatocellular carcinomas. Because HIV causes immunosuppression and because most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. NIH-supported investigators are trying to clarify the mechanistic role of chronic stimulation mediated by viral and cellular proteins, high levels of growth-promoting cytokines present in HIV-infected subjects, and human DNA and RNA viruses and their direct or indirect interaction with HIV in the development of AIDS-associated malignancies. Studies of AIDS-related KS have highlighted the potential causative role of a newly discovered human herpesvirus (HHV-8), angiogenic growth factors, and HIV proteins released in the extracellular milieu in the etiology of this neoplasm. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate to the identification of new targets for prevention and treatment.

Following the introduction of effective ART, preliminary studies have shown dramatic declines in the incidence of KS and primary central nervous system (CNS) lymphoma and small decreases in non-Hodgkin's lymphoma (NHL). However, increased incidence of anal dysplasia and increased persistence of HPV in HIV-infected individuals have been reported; ART appears to have little effect on the natural history of HPV-mediated anogenital lesions. More extensive followup is

needed to clearly discern the impact of effective therapy and prolonged survival of HIV-infected persons on their risk of developing cancer. Also needed is a better identification of the spectrum of malignant diseases that are associated with HIV infections, especially as HIV-infected individuals are living longer with subclinical immune deficiency.

Neuropathogenesis

Neurological disease and neurobehavioral dysfunction associated with HIV infection cause considerable morbidity and mortality in afflicted children and adults. These manifestations include diseases associated with opportunistic infection of the brain resulting from the underlying immunodeficiency and the AIDS dementia complex, a disorder that is unique to HIV infection. HIV enters the CNS very early during infection, although manifestation of neurologic impairment occurs in late-stage HIV infection. Intense research efforts have focused on elucidating the role of HIV persistence in the brain parenchyma in the development of CNS disease. The cells expressing HIV or SIV in patients or monkeys with AIDS have been found to be primarily perivascular macrophages, that is, cells derived from monocytes trafficking to the brain that have a very rapid turnover. These findings raise the intriguing possibility that the viral reservoir in the CNS is not composed of persistently or latently infected cells but of cells undergoing continual turnover. NIH-supported research is directed at understanding how HIV infection contributes to nervous system damage through direct interaction of HIV with neuronal and nonneuronal cells and indirect mechanisms, such as those mediated by cytokine, chemokine, and neurotoxins released in response to the infection or the local inflammatory response to infection. Important areas of ongoing research include identifying how HIV enters and establishes infection in the different compartments of the CNS, defining the immune or other mechanisms that control HIV replication within the CNS, elucidating the mechanisms of neuropathogenesis, developing treatments for individuals suffering from HIV-related CNS and neurological disorders, and determining the incidence and severity of neurologic complications in treated and untreated populations. The possible role of the CNS as a reservoir of HIV infection in the setting of ART with limited CNS bioavailability also is under investigation. Special emphasis in all these studies is given to *in vivo* models of neuropathogenesis and to the integration of basic research studies on the neurologic complications of AIDS with natural history studies and ongoing clinical trials.

Opportunistic Infections and Coinfections

HIV infection results in progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-1-infected individuals. OIs can affect virtually every tissue and organ system

in the body, resulting in severe functional compromise. The NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated OIs. Priority is given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals (e.g., tuberculosis [TB]) or (b) contribute significantly to HIV transmission or acquisition (e.g., herpes simplex virus [HSV]-2). Currently supported research is directed toward developing animal models to study disease pathogenesis, identifying new targets for therapeutic interventions, and facilitating discovery and development of prophylactic and therapeutic agents. Special emphasis is given to the interactions between the pathogen and the host and its immune system. This research will permit a better understanding of the establishment of infection, mechanisms of immune control by the host, evasion by the pathogen, and the contribution of the host immune response to disease.

The use of potent ART has resulted in a dramatic decline in the incidence of OIs in HIV-infected persons, suggesting that the increase in the number of immune cells that follows effective ART is accompanied by the recovery of functional responsiveness to antigens of several important opportunistic pathogens. However, development of OIs during the first 2 months of effective ART has also been described, suggesting that the restoration of immune function may be partial or delayed. As a result of reconstitution of their immune responses, new manifestations also have been reported in HIV-infected persons taking anti-HIV drugs.

OIs remain one of the most important complications of HIV infection and the principal cause of death in AIDS patients, especially in developing countries. Understanding the fundamental biology and pathogenesis of these organisms, their interaction with the host immune system, and the effect of therapy-associated immune reconstitution on the clinical course and manifestations of OIs will translate into new or more rational approaches to the prevention and treatment of OIs in patients on ART, as well as in patients who lack access to or who are not responding to ART.

As the classic OIs that were the hallmark of HIV/AIDS have increasingly become less frequent in the developed world as a result of the introduction of effective ART and the use of OI prophylaxis, coinfections, defined as those infections that may precede HIV infection, have emerged as important complications in HIV infection. Hepatitis B and C virus (HBV and HCV) coinfections are becoming increasingly prevalent in HIV-infected patients in developed countries, and epidemiologic studies have indicated that chronic liver disease now represents a major cause of morbidity and mortality in this population. Infection with HPV, which causes genital warts and can lead to cervical and anal cancers, occurs with increased frequency in HIV-infected women worldwide. Precancerous conditions associated with HPV also are more common and more severe in HIV-infected women and adolescents. Worldwide,

TB is a key coinfection suffered by the HIV-infected, and the numbers of TB cases in the world are rising, driven in large part by the HIV epidemic. Furthermore, the impact of endemic parasitic infections in the developing world, which are known to influence the immune response, is not clear with respect to HIV transmission or disease progression. On the other hand, there are data to suggest that certain coinfections (e.g., scrub typhus, GB virus C, and HHV-6) may interfere with HIV replication. There is a clear need to conduct research directed at assessing the impact of the most prevalent coinfections on immune dysfunction and HIV progression and likewise the impact of HIV infection on the natural history and pathogenesis of coinfecting pathogens.

Organ System-Specific Complications of HIV Infection

Organ system-specific manifestations also attend HIV infection and disease. Gastrointestinal (GI) dysfunction and malabsorption are commonly observed in HIV-infected subjects. The GI tract is one of the most important routes of transmission of HIV and appears to be a major site of viral replication and the major site of CD4+ T-cell depletion in early stages of infection in the SIV model. NIH-supported researchers are investigating the contribution of OIs, of micronutrient deficiencies, of acquired deficiencies in intestinal enzymes, of malignancies, and of potential HIV infection of cells in the GI tract to the GI complications observed in HIV-infected individuals.

HIV infection is also associated with multiple endocrine alterations, probably reflecting critical interaction between the endocrine and the immune systems. HIV-associated hematologic, pulmonary, cardiac and vascular, renal, mucocutaneous, bone, and liver complications also represent causes of morbidity in infected subjects. Some of these complications are disproportionally affecting racial groups. For instance, HIV-associated nephropathy, the most common cause of chronic renal failure in HIV-infected individuals, occurs almost exclusively in African Americans and represents the third most common cause of end-stage renal disease in this population. The pathogenic mechanisms involved in all these AIDS manifestations are not well understood and are under investigation. Their definition will permit a more rational approach to both preventive and therapeutic interventions.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Delineate the viral, host, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

STRATEGIES:

- Determine the role of phenotype/genotype/fitness and dose on transmission of cell-free and cell-associated HIV, in various bodily fluids at different portals of entry.
- Determine mechanisms by which virus-encoded genes and viral gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the structures and interactions of viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
- Delineate the mechanisms by which host-encoded genes and gene products regulate HIV replication and influence transmission, establishment, and spread of HIV infection.
- Determine the cells, molecules, and tissue types that serve as portals of entry and support subsequent spread of HIV.
- Delineate the mechanisms by which innate and adaptive immunity influence HIV replication and modulate transmission, establishment, and spread of HIV infection.
- Investigate the role of inflammation and its mediators in tissue on HIV transmission and dissemination.
- Delineate the mechanisms by which STIs and coinfections influence HIV transmission, replication, establishment, and spread of HIV infection.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV infection.

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative as well as functional virologic and immunologic assays.
- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.
- Develop and utilize natural and innovative technologies to procure, maintain, and expand the macaque model of AIDS and facilitate collaborative research using this model.

OBJECTIVE - B:

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction and disease progression in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

STRATEGIES:

- Define the factors that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint.
- Determine how early events that regulate the establishment and systemic spread of HIV infection define the later clinical course of the disease in HIV-infected populations.
- Define the virologic, host, pharmacologic, copathogens, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, host cellular factors, and intracellular compartments regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of viral and host proteins involved in the processes that underlie HIV disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and NHP models, focusing on:
  - the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - the impact of HIV infection on T-cell population numbers, specificities, and functions;

  - HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;
  - the structural and functional compromise of primary and secondary lymphoid organs including hematopoietic precursor cells and their microenvironment;
  - influences on the developing immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.

- Evaluate whether and to what extent viral-induced damage to the immune system can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the lifespan and developmental and regenerative pathways of T lymphocytes in humans and NHP models; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with age.
- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Define the reservoirs of virus infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the immunopathogenesis of HIV infection.
- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

OBJECTIVE - C:

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic and body composition changes in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES:

- Define the mechanisms underlying alterations in metabolism, body composition, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, and bone disease to determine:
  - the effects of antiviral therapies and suppression of virus replication;
  - the influence of disease stages;
  - the contributions of individual virologic and host factors, including genetic loci; and
  - the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, and the long-term risks of diabetes, bone disease, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, and the long-term risks of diabetes, bone, and atherosclerotic cardiovascular disease.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, and bone research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, and bone research.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the metabolic, endocrine, cardiovascular, and bone disease complications associated with HIV infection and treatment.

- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, and bone complications.
- Integrate metabolic, endocrine, cardiovascular, and bone studies into ongoing and planned treatment trials.

OBJECTIVE - D:

Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES:

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of HIV-associated malignancies.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of cancer and preneoplastic lesions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Elucidate whether the mechanisms by which HIV-associated cancers and the same cancers that develop in HIV-seronegative individuals are shared or different.
- Identify the host factors that increase the risk of HIV-associated malignant disease.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the manifestations of HIV-associated malignancies are altered by such therapies.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE - E:

Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES:

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction including:
  - identifying how HIV enters, establishes infection, spreads, and persists in the CNS;
  - examining the effects of HIV infection on specific cell populations and regions of the nervous system;
  - investigating the connection between blood-brain barrier dysfunction and neuronal injury in the context of HIV infection;
  - determining the relationship of virologic (including distinct subtypes of HIV), host (including the genetics of the virus/host interactions), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis (including peripheral neuropathies);
  - determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment.
- Determine the impact of HIV/CNS infection on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.

- Define mechanisms of immunologic control of HIV, OIs, and coinfections in the CNS.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders.
- Investigate aspects of HIV infection that uniquely influence the developing nervous system.
- Delineate the role of OIs, coinfections, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., NHP models) of CNS HIV/SIV infection that best reflect specific aspects of the human HIV/CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of treatment trials.

OBJECTIVE - F:

Elucidate the pathogenic mechanisms and consequences of OIs and coinfections in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals (e.g., TB) or (b) contribute significantly to HIV transmission or acquisition (e.g., HSV-2).

(The scientific objectives C through G are of equal weight.)

STRATEGIES:

- Conduct studies of the basic biology of such opportunistic pathogens and their interaction with the host.
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs in HIV-infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens.
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and coinfections.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by ART therapies.
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV-infected subjects.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs, including stable, inexpensive, easy-to-perform assays appropriate for use in developing countries.

OBJECTIVE - G:

Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES:

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - GI, including liver and biliary, diseases,
  - nephropathy,
  - endocrine dysfunction,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cardiac and vascular disease,
  - cutaneous disease,
  - oral disease, and
  - other organ/tissue-specific disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of HIV/SIV-associated disorders in the above systems.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, genomics, and proteomics to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials.

FY 2007 OAR
Planning Group for
Etiology and Pathogenesis

FY 2007 ETIOLOGY AND PATHOGENESIS PLANNING GROUP

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